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(54) Calcitonin-containing emulsion for nasal administration.

(57) The present invention is to provide emulsion preparations for nasal administration containing calcitonins, which are safely and effectively administered, compared with the conventional calcitonin preparations. The emulsions are prepared by using a calcitonin as the active ingredient, an azacycloalkane derivative as the absorption promotor such as 1-[2-(decylthio)ethyl] azacyclopentan-2-one, and glycyrrhizic acid or its salt.

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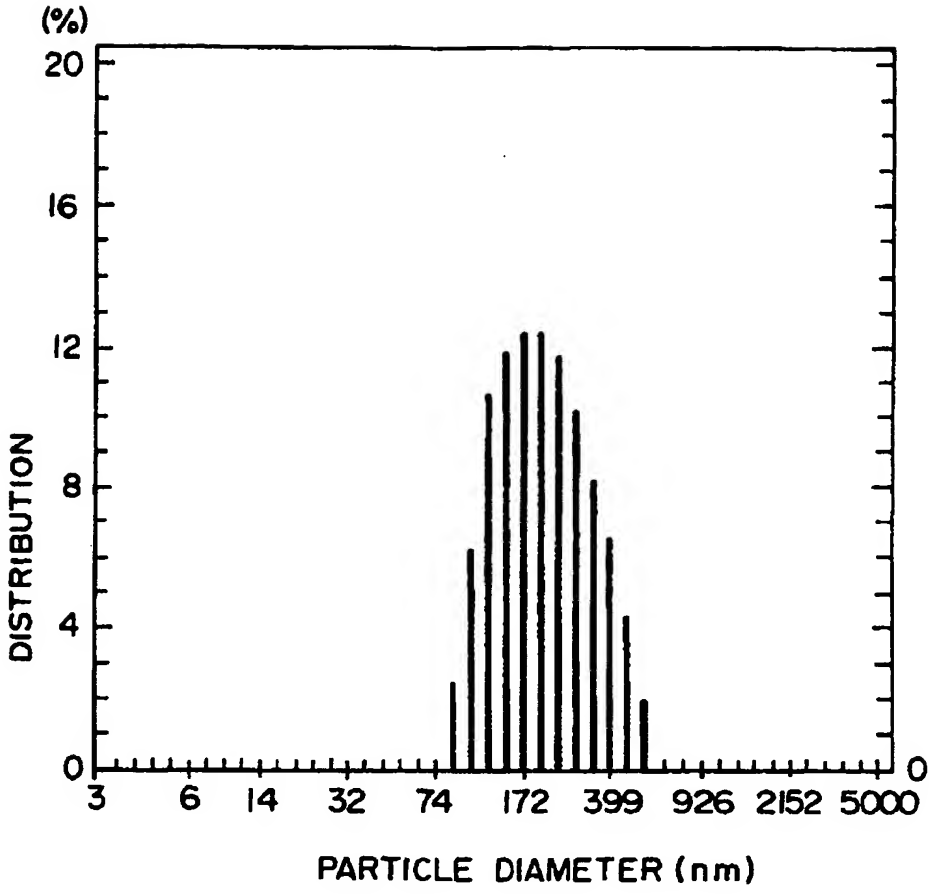
FIG. 1


(%)
20
16
12
8
4
0
DISTRIBUTION
3
6
14
32
74
172
399
926
2152
5000
0
PARTICLE DIAMETER (nm)

The present invention relates to an emulsion for nasal administration containing a calcitonin as the active ingredient. Particularly, it relates to such emulsion for nasal administration, having superior stability, and being so improved that the calcitonin is absorbed safely and efficiently through sprapying administration in the nasal cavity.

Physiologically active peptides are becoming one of the fields where the most progressive development is effected as future therapeutic drugs. However, the present common route of administration for the peptide drugs are almost limited to injection. Thus, a more simple administrating preparation which can be administered by self-medication has been desired, especially in the treatments of the chronic disorders, to avoid the inconvenient of going to hospital regularly, and for the purpose of diminishing pain and anguish at the site of injection.

Recently, there have been many attempts to develop alternative administration, e.g. rectal, nasal, oral and etc., instead of injection route. It has been found that even peptides, which are poorly absorbed in the form of a normal drug preparation, are promotedly absorbed by addition of a surface active agents, and several absorption promotors have been found.

Among various physiologically active peptides now used as therapeutic drugs, calcitonins are generally known as a peptide hormone having hypocalcemic activity inhibition of bone resorption and anti-ulcer actions, and are used clinically as therapeutic drugs for various hypercalcemia, Paget's disease, and osteoporosis. But, it has been known that calcitonins are a highly hydrophillic peptide with a higher molecular weight (as high as about 3,400) and much poorly absorbed through the gastrointestinal system. Accordingly, absorption through nasal mucosa using a nasal administration preparation with an absorption promotor has been tried, and such nasal administration preparations utilizing a surface active agent or a bile acid salt as the absorption promotor have been reported. For example, the Japanese Unexamined Patent Publication Nos. 89,619/1984 and 130,820/1984 disclosed the use of surface active agents. Using salmon calcitonin, H. Hanson et al reported in "Delivery system for Peptide Drugs, Plenum Press," (1986), pages 233-242 that the calcitonin which is poorly abosrbed in the form of a normal preparation, is promotedly absorbed by additon of a surface active agent or bile acid.

However, these preparations are not satisfactory due to the inferior absorbability and local irritaion and not yet practically employed. Thus, the absorption promotors having more absorption promoting effect with higher safety are desired.

While,the Japanese Unexamined Patent Publication No. 238,261/1987 disclosed that azacycloalkane derivatives exhibit superior absorption promoting effect. It was found that these derivatives have much stronger absorption promoting effect with physical properties different from those absorption promotors used in the conventional preparations for nasal administration. Accordingly, calcitonin preparations for nasal administration were prepared using such derivatives as the absorption promotor, but satisfactory results were not obtained since the emulsifiable agent required for emulsification, heretofore used, were insufficiently worked.

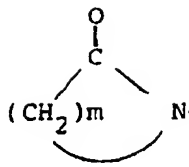
Also, many studies have been conducted recently on emulsions which are a liquid preparation containing water and oil in homogeneous state. Many emulsifying agents have been developed, and much stable emulsions have been broadly used, owing to the significant progress in emulsifying techniques.

However, the majority of the emulsions are those using a nonionic surface active agent having a polyoxyethylene chain, or an ionic surface active agent, as the emulsifying agent, many of which are, in turn, felt cocern about the safety to human body. Further, egg-yolk lecithin and soy bean lecithin may be referred to as the emulsifying agent commonly used for fatty emulsions for intravenus injection. These emulsions have, however, certain problems in their insufficient stability at room temperatures, as well as their homogeneity.

The present invention has been accomplished in order to deal with such problems, and an object of the present invention is to provide a calcitonin emulsion preparation for nasal administration having excellent stability, when using an azacycloalkane derivative as the absorption promotor.

As the results of studies on emulsifying agents suitable to such emulsion preparations, the present inventors have found that glycyrrhizic acid or its non-toxic salt, which has been thought to have a weak solubilizability, is unexpectedly well suited for the emulsification of calcitonin nasal administration preparations using an azacycloalkane derivative as the absorption promotor, stronger than nonionic surface active agents such as HCO-60 and Tween 80, thus yielding a stable emulsion with homogeneous fine particles.

Thus, the present invention relates to a calcitonin-containing emulsion for nasal administration, which is characterized by having a calcitonin as the active ingredient, and containing, at least, an azacycloalkane derivative of the general formula [1] :



[1]

(wherein R is an alkyl residue, m is an integer of 2-4, and n is an integer of 1-15, provided that R is an alkyl residue with a carbon number of 5-11 in case where n is 1-3,) as the absorption promotor, glycyrrhizic acid or its non-toxic salt, and a suitable amount of water.

Calcitonins as the active ingredient in the present invention are commonly known as a peptide hormone having hypocalcemic activity inhibition of bone resorption and anti-ulcer actions, and are used clinically as therapeutic drugs for various hypercalcemia, Paget's disease, and osteoporosis. Naturally occurred calcitonins and their synthetic derivatives are known. As natural ones, eel calcitonin, salmon calcitonin, porcine calcitonin, human calcitonin, chicken calcitonin, etc. are illustrated. As synthetic ones, [ASU$^{1-7}$] eel calcitonin (WHO generic name: elcatonin), [ASU$^{1-7}$] chicken calcitonin, [ASU$^{1-7}$] salmon calcitonin and [ASU$^{1-7}$] human calcitonin, etc. are illustrated. Elcatonin is accordingly the most preferred calcitonin for use in accordance with the present invention. Other calcitonin peptides than those above mentioned may be employed in the present invention as far as they have a hypocalcemic activity.

Ordinary calcitonin concentration in the calcitonin emulsion for nasal administration is 10-10,000 International Units, more preferably, 100-1,000 International Units, per milliliter of the preparation.

The azacycloalkane derivatives used as the absorption promotor in the present invention are an oily material, which are included in the above general formula [1] and illustrated in the Japanese Unexamined Patent Publication No. 238,261/1986. As embodiments of the R in the general formula [1], straight chain or branched alkyl residues, such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicocyl, etc. may be mentioned. Among them, the preferred absorption promotor is 1-[2-(decylthio)ethyl]azacyclopentane-2-one (oil); R being an alkyl residue with a carbon number of 10, m =3 and n=2, in the general formula [1].

The amount of such azacycloalkane derivative to be added in the present invention is preferably so as to give a concentration of 0.01%-10% (W/V), more preferably, 0.1%-5% (W/V).

Glycyrrhizic acid and its non-toxic salts, used in the present invention, are known as a natural constituent extracted from licorice (Glycyrrhiza glabra), and widely used for cosmetics and food additives such as sweetening agents.

As the glycyrrhizic acid and its non-toxic salts, there may be illustrated glycyrrhizic acid, and dipotassium glycyrrhizate, monoammonium glycyrrhizate, disodium glycyrrhizate, trisodium glycyrrhizate, and the like. The amount to be added of such acid or its salt may be so as to give a concentration of not less than 0.1% (W/V), ordinarily 0.1%-5%, more preferably 0.5%-2%, in the preparation.

In general, preparation for nasal administration are conveniently an aqueous liquid formulation either in spray or in drop form. The emulsions of the present invention may be prepared by using, at least, the above-mentioned oily azacycloalkane derivative, glycyrrhizic acid or its non-toxic salt, and a suitable amount of water to give concentrations of the above constituents as mentioned above. They are preferably adjusted to a pH of 5-7 and an osmotic pressure ratio against physiological salt solution of about 1. To adjust or maintain pH 5-7, a pH adjusting agent such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium hydrogencarbonate, hydrochloric acid, sulfuric acid, or a buffer solution such as acetate, lactate, citrate and phosphate buffer solutions, may be added. To adjust the osmotic pressure ratio to approximately 1, an isotonic agent, preferably glycerol, may be used. If required, sodium chloride, potassium chloride, mannitol, glucose, and the like, may be added.

The composition of the invention may also contain a appropriate preserving agent as conventional pharmaceutically acceptable excipient. For example, p-oxybenzoate esters, chlorobutanol, phenylethyl alcohol, benzalkonium chloride, phenol, thimerosal, dehydroacetic acid, sorbic acid, and the like, are illustrated. Suitable concentration of such preserving agent is, generally, 0.02%-2% (W/V), varying depending on the kind selected.

Emulsions for nasal administration can be prepared by mixing each ingredients in an arbitrary sequence and emulsifying the mixture, according to the well-known procedures. To prepare the emulsions of the present invention, for example, dipotassium glycyrrhizate, a calcitonin, and other additives to be used in the present invention, are added with a suitable amount of distilled water for injection purpose, and the mixture is made to a solution by heating and agitation. Then, the solution is adjusted to a desired pH by addition of a pH adjustor, for example, sodium hydroxide or hydrochloric acid. After addition of an azacycloalkane derivative as the

absorption promotor, the mixture may be allowed to emulsify by the conventional method using an emulsifier. For example, use of Biomixer (NIHON SEIKI SEISAKUSHO) with 10,000 rpm agitation for 10 minutes yields a homogeneously dispersed emulsion with 0.1-0.3 μm fine particle size. Also, ultrasonic emulsifier and colloid mill, among others, may be used for the preparation. Altanatively, the calcitonin may be added after the preparation of the emulsion and allowed to dissolve in it. The resulting homogeneous calcitonin-containing emulsion preparation may be filtered in asepic condition, for example, through a 0.22 μm membrane filter, and filled, for example, in vials to give the final product.

The dosage of the emulsion of the present invention varys depending on the administrating objects, but, in case of human, the administration is secured by spraying the emulsion to a naris or nares using a metered-dose spray (0.05%-0.1 ml/stroke) each one or twice time and 1-3 times a day.

One object of the calcitonin emulsion for nasal administration of the present invention is to administer the emulsion in the nasal cavity in the state of mist using conventional spraying apparatus, thereby to secure the systemic effect. Using the preparation of the present invention, it is possible to make calcitonin to distribute in the whole body through adhesion of the emulsion in the wide area of the nasal mucosa and substantial permeation through the mucosa. Accordingly, the calcitonin-containing emulsion for nasal administration of the present invention can be administered to patients having disorders needing the treatment with calcitonins, even by themselves, without problems such as pain and anguish when administered by injection.

The present invention will be more fully explained with respect to the following experimental and working examples, which are, however, not construed to be limitative.

Figure 1 shows average particle diameter and size distribution of the Preparation C prepared according to the present invention.

Figure 2 shows elcatonin plasma levels versus time after nasal administration of elcatonin (80 units) to the beagle dogs (n=4).

Example 1

Stabilities of emulsions

<<Experimental method>>

Using 1-[2-(decylthio)ethyl]azacyclopentan-2-one chosen from the azacycloalkane derivatives, and three emulsifying agents as follows, emulsifiabilities and stabilities of the emulsions were examined:

(1) Dipotassium glycyrrhizate (MARUZEN KASEI)

(2) HCO-60 (NIKKO Chemicals)

(3) Tween 80 (NIKKO Chemicals)

Each 0.1 g of 1-[2-(decylthio)ethyl]azacyclopentan-2-one was placed in a test tube (10 ml), and thereto was added 5.0 ml of an aqueous solution prepared preliminarily by dissolving each of the above three emulsifying agents in a concentration of 0.1-0.5% (W/V), or water containing none of such agent. The mixture was agitated under 15,000 rpm for 1 minute by Biomixer (NIHON SEIKI SEISAKUSHO) to prepare each emulsion. The state of dispersion just after the preparation and after 3 days standing at room temperature was observed. The turbidity just after the preparation was measured by extinction at 650 nm, and used as the index of emulsifiability.

<<Results>>

The results are shown in Table 1-3. As obvious from the tables, dipotassium glycyrrhizate of the present invention exhibited at least good emulsification at 0.1-5% and gave full dissolution at 4-5%. The control which contained no dipotassium glycyrrhizate gave two phases separated just after the preparation. Further, the stabilities of the emulsions after 3 days at room temperature were observed. Separation of the two phase were recognized in emulsions prepared using lower concentrations of HCO-60 and Tween 80.

While, as for the turbidity as the index of emulsifiability, dipotassium glycyrrhizate showed lower values, that is, stronger emulsifiability, than HCO-60 and Tween 80 when compared at the same concentration level. These results show that dipotassium glycyrrhizate is significantly superior in its emulsifiability and stability of the emulsion to HCO-60 and Tween 80 which are emulsifying agent widely used now as the additives for pharmaceuticals.

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Table 1

(Use of dipotassium glycyrrhizate)

Concentrations (%)	Just after preparation	After 3 days standing	Turbidity * (650 µm)
5.0	Colorless clear	Colorless clear	0.006
4.0	Colorless clear	Colorless clear	0.006
3.0	White clear	White clear	0.346
2.0	White clear	White clear	0.405
1.0	White clear	White clear	0.437
0.5	White clear	White clear	0.459
0.1	White emulsified	White emulsified	1.284
Not added	Separated two phases	Separated two phases	-

Table 2

(Use of Tween 80)

Concentrations	Just after preparations	After 3 days standing	Turbidity* (650 µm)
5.0	White clear	White clear	0.172
4.0	White clear	White clear	0.165
3.0	Whtie clear	Whtie clear	0.244
2.0	Whtie clear	White clear	0.803
1.0	White emulsified	White emulsion separated	1.119
0.5	White emulsified	White emulsion separated	2.619

Table 3

(Use of HCO-60)

Concentrations	Just after preparation	After 3 days standing	Turbidity* (650 μm)
5.0	White clear	White clear	0.317
4.0	White clear	White clear	0.425
3.0	White clear	White clear	0.712
2.0	White clear	White clear	0.915
1.0	White emulsified	White emulsion partially separated	2.829
0.5	White emulsified	White emulsion partially separated	2.877

*Turbidity (650 μm) 0 - 0.1: colorless transparent
0.1 - 1.0:white transparent
(backside visible when looking through)
1.0 - : white emulsified
(emulsion like commercially available milk)

Example 2

Stabilities of the emulsions relating to the added concentrations of the azacycloalkane derivative

<<Experimental method>>

Each 5 ml of a 1% (W/V) solution preliminarily prepared by dissolving dispotassium glycyrrhizate in distilled water was poured in each of 8 10-ml-test tubes, and thereto was added 1[2-(decylthio)ethyl]azacyclopentan-2-one chosen from the azacycloalkane derivatives so as to make a concentration ranging from 0 to 10%. Then, the mixture was agitated for 1 minute using Biomixer (NIHON SEIKI SEISAKUSHO) (15,000 rpm), to prepare each emulsion. The state of dispersion just after the preparation, or after 3 days or 7 days standing at room temperature was observed.

<<Results>>

The results are shown in Table 4. As obvious from the table, using 1% dipotassium glycyrrhizate of the present invention, 1-[2-(decylthio)ethyl]azacyclopentan-2-one among the azacycloalkane derivatives exhibited at least good emulsification and gave stable emulsion, within a concentration ranging from 0.01% to 10%.

Table 4

Stabilities of emulsions relating to the added concentrations of 1-[2-(decylthio)ethyl]azacyclopentan-2-one

Concentrations (%)	Observation just after preparation	Observation after 3 days standing	Observation after 7 days standing
10.0	White emulsified	White emulsified	White emulsified
5.0	White emulsified	White emulsified	White emulsified
2.0	White clear	White clear	White clear
1.0	White clear	White clear	White clear
0.5	Colorless clear	Colorless clear	Colorless clear
0.1	Colorless clear	Colorless clear	Colorless clear
0.01	Colorless clear	Colorless clear	Colorless clear
0	Colorless clear	Colorless clear	Colorless clear

Furthermore, a calcitonin-containing emulsion for nasal administration was prepared, and its stability was comparatively examined.

Example 3

Thermal stability of calcitonin emulsion for nasal administration

Composition of the present invention:	
Ingredients per 1 ml of emulsion;	
elcatonin	400 Units
1-[2-(decylthio)ethyl]azascyclopentan-2-one	20 mg
dipotassium glycyrrhizate	10 mg
glycerol	22 mg
methyl p-oxybenzoate	1.0 mg
sodium hydroxide	to pH 6
distilled water (for injection)	to make the volume 1 ml

Control (a):	
Ingredients per 1 ml of emulsion;	
elcatonin	400 Units
1-[2-(decylthio)ethyl]azacyclopentan-2-one	20 mg
HCO-60	10 mg
glycerol	22 mg
methyl p-oxybenzoate	1.0 mg
sodium hydroxide	to pH 6
distilled water (for injection)	to make the volume 1 ml

Control (b):	
Ingredients per 1 ml of emulsion;	
elcatonin	400 Units
1-[2-(decylthio)ethyl]azacyclopentan-2-one	20 mg
Tween 80	10 mg
glycerol	22 mg
methyl p-oxybenzoate	1.0 mg
sodium hydroxide	to pH 6
distilled water (for injection)	to make the volume 1 ml

Emulsion compositions with the ingredients as mentioned above were prepared and subjected to severity

tests. Appearances of the emulsions were examined and the contents of elcatonin were quantitated by HPLC method. The results are shown in Table 5. As obvious from the table, Controls (a) and (b) showed separation to two phases according to the lapse of time during the severity test at 50°C. While, the emulsion of the present invention was kept stably in the emulsified state until the end of 3 months. It was also found that elcatonin in the emulsion of the present invention was maintained satisfactorily, compared to that in the Controls (a) and (b).

Table 5

Stabilities of emulsions after 50°C severity tests

Examples	Tested items	Just after	1 month	2 months	3 months
Composition of the invention	Appearance	White emulsion	White emulsion	White emulsion	White emulsion
	Residual ratio (%)	100	96.2	93.8	87.4
Control (a)	Appearance	White emulsion	White emulsion	Separated two phases	Separated two phases
	Residual ratio (%)	100	87.4	82.2	76.3
Control (b)	Appearance	White emulsion	Separated two phases	Separated two phases	Separated two phases
	Residual ratio (%)	100	75.8	56.9	49.2

Example 4

Absorption test of beagles

(1) Preparation of composition for nasal administration containing elcatonin

① Control preparation Ⓐ

Paraben solution: A Paraben solution was prepared in advnace by adding 2.4 g of methyl p-oxybenzoate and 600 mg of propyl p-oxybenzoate in 2000 ml of distilled water for injection, and making the mixture to dissolve under agitation at 80°C.

Into a 500 ml-volume beaker was placed 100 ml of the Paraben solution. After adjusting the temperature to 40°C, 4.4 g of glycerol and 2 g of dipotassium glycyrrhizate were added thereto. After confirming the homogeneous dissolution, the solution was adjusted to pH 6.0 with 1 N sodium hydroxide, and then the volume was made up to 200 ml with the Paraben solution. After addition of 16 mg of elcatonin (specific activity, 5,446 Units/mg), the mixture was slowly agitated to make a solution, which was then filtered aseptically (a membrane filter of 0.22 μm) and filled aseptically into 3 ml vials adaptable to a mechanical spray for nasal administration to give the final preparation. This composition contained 400 Units/ml of elcatonin, and one stroke of the adapter accurately administered 40 Units.

② Preparation Ⓑ

Into a 500 ml-volume beaker was placed 100 ml of the Paraben solution prepared as above. After adjusting the temperature to 40°C, 4.4 g of glycerol and 2.0 g of dipotassium glycyrrhizate (MARUZEN KASEI) were added thereto. After confirming the homogeneous dissolution, 2.0 g of 1-[2-(decylthio)ethyl]azacyclopentan-2-one was added thereto, and the pH was adjusted to 6.0 with 1 N sodium hydroxide. Then, the total volume was made up to 200 ml with the Paraben solution as prepared above, followed by emulsification through agitation using Biomixer (NIHON SEIKI SEISAKUSHO: Type ABM) generator shaft (BM-4) at 10,000 rpm for 5 minutes, thereby to obtain an emulsion. After addition of 16 mg of elcatonin (specific activity, 5,446 Units/mg), followed by slow agitation for dissolution, the resulting emulsion was aseptically filtered (membrane filter of 0.22 μm), and filled aseptically in each 3 ml vials adaptable to a mechanical spray for nasal administration, thereby to obtain the final preparation. This composition contained 400 Units/ml of elcatonin, and one stroke of the adapter accurately administered 40 Units.

③ Preparation Ⓒ

Using 4.0 g of 1-[2-(decylthio)ethyl] azacyclopentan-2-one and with otherwise the similar procedure to Preparation B, a preparation for nasal administration containing 400 Units/ml elcatonin was prepared.

④ Preparation Ⓓ

Using 6.0 g of 1-[2-(decylthio)ethyl] azacyclopentan-2-one and with otherwise the similar procedure to Preparation B, a preparation for nasal administration containing 400 Units/ml elcatonin was prepared.

⑤ Preparation Ⓔ

Using 10.0 g of 1-[2-(decylthio)ethyl] azacyclopentan-2-one and with otherwise the similar procedure to Preparation B, a preparation for nasal administration containing 400 Units/ml elcatonin was prepared.

(2) Average particle diameter and particle size distribution of the emulsion of the present invention

Laser particle diameter analyzing system: Using LPA-3000/3100 (OHTSUKA DENSHI KABUSHIKI KAISHA), the average particle diameter and particle size distribution of the Preparation C were examined. (The results are shown in Figure 1.)

(3) Nasal administration tests to beagles

Male beagles (n=4), each weighing approximately 10 kg were used, and then the present study was per-

formed under non-anesthetized condition. Nasal administration was conducted by inserting a nozzle (our hand made) for metered-dose spray for nasal administration into the nasal cavity of the dogs, and spray-administering each 0.1 ml amount to each of both nares. As the control, a commercially available elcatonin-injection (40 Units) was intramuscularly injected (femoral region). Each 2.5 ml of the blood was collected in a heparinized syringe from the foreleg vein just before administration at intervals of 5, 10, 20, 30, 45, 60 and 120 minutes after administration of Elcatonin. After the collection, the plasma was separated by centrifugation (3,000 rpm) for 10 minutes, and was kept frozen at -30°C until used for the assay. Elcatonin plasma level were evaluated by a RIA method, with a detection limit of 25 pg/ml.

(4) Results

① Average particle diameter and particle size distribution of the emulsions of the present invention

Particle size distribution chart with respect to the Preparation C which is a typical example of the present invention is shown in Figure 1, in which the average particle diameter is 192.3 μm. Thus, the present emulsion is found to have ideal particle diameter and size distribution as nasal administration emulsion, when considered from the stability and the nasal absorbability. Preparations B, D and E also exhibited ideal particle diameter and size distribution, while, Control Preparation A remained in the state of solution.

② Nasal administration tests to beagles

In the nasal administration of the emulsions of the present invention using elcatonin, one of calcitonins, the absorptions of the elcatonin concerning the elcatonin concentration in plasma are shown in Figure 2. Comparison is made with the administration by intramuscular injection, which is shown by broken lines in the figure. Nasal administration of Control Preparation A without 1-[2-(decylthio)ethyl]azacyclopentan-2-one, a kind of azacycloalkane derivatives showed plasma elcatonin level under the detection limit. While, Preparations B, C, D and E which contain 1-5% of 1-[2-(decylthio)ethyl]azacyclopentan-2-one exhibited much satisfactory absorptions. Thus, it is obvious that the emulsions of the present invention have significantly improved the nasal elcatonin absorbability when compared with Control Preparation A, and are proved to be a useful preparation in place of intramuscular administration, due to the superior biological availability.

In Figure 2,

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- · · ○ · · · shows the results of intramuscularly administering elcatonin (40 Units/dog) as the control,
- — □ — shows the results of nasal administration of control Preparation A (0%) obtained in ① of example 4,
- — △ — shows the results of nasal administration of Preparation B (1%) obtained in ② of example 4,
- — ◇ — shows the results of nasal administration of Preparation C (2%) obtain in ③ of example 4,
- — ☓ — shows the results of nasal administration of Preparation D (3%) obtained in ④ of example 4, and
- — + — shows the results of nasal administration of Preparation E (5%) obtained in ⑤ of example 4.

Preferable working examples of the calcitonin emulsion for nasal administration of the present invention will be described below.

Example 5

Emulsions for nasal administration were prepared using the following amounts (per 1 ml) of ingredients:

①	elcatonin	each 100, 200 and 400 Units
②	1-[2-(decylthio)ethyl] azacyclopentan-2-one	10 mg
③	dipotassium glycyrrhizate	10 mg
④	glycerol	22 mg
⑤	benzalkonium chloride	0.1 mg
⑥	sodium hydroxide	to pH 6
⑦	distilled water for injection	a volume to make 1 ml

The resulting emulsions were aseptically filtered (a membrane filter of 0.22 μm), and aseptically filled in each 3 ml vials adaptable to a mechanical spray for nasal administration, to obtain the final preparation. These compositions contained 100-400 Units/ml of elcatonin, and a stroke of the adaptor accurately administered 10-40 Units.

Example 6

Emulsions for nasal administration were prepared using the following amounts (per 1 ml) of ingredients:

①	elcatonin	each 200, 400 and 800 Units
②	1-[2-(decylthio)ethyl] azacyclopentan-2-one	10 mg
③	dipotassium glycyrrhizate	10 mg
④	sodium chloride	8.0 mg
⑤	methyl p-oxybenzoate	1.0 mg
⑥	sodium hydroxide	to pH 6
⑦	distilled water for injection	a volume to make 1 ml

The resulting emulsions were aseptically filtered (a membrane filter of 0.22 μm), and aseptically filled in each 3 ml vials adaptable to a mechanical spray for nasal administration, to obtain the final preparation. These compositions contained 200-400 Units/ml of elcatonin, and a stroke of the adaptor accurately administered 20-80 Units.

Example 7

Emulsions for nasal administration were prepared using the following amounts (per 1 ml) of ingredients:

①	elcatonin	each 100, 200 and 400 Units
②	1-[2-(decylthio)ethyl] azacyclopentan-2-one	20 mg
③	monoammonium glycyrrhizate	10 mg
④	sodium chloride	8.0 mg
⑤	methyl p-oxybenzoate	1.0 mg
⑥	sodium hydroxide	to pH 6
⑦	distilled water for injection	a volume to make 1 ml

The resulting emulsions were aseptically filtered (a membrane filter of 0.22 μm), and aseptically filled in each 3 ml vials adaptable to a mechanical spray for nasal administration, to obtain the final preparation. These compositions contained 100-400 Units/ml of elcatonin, and a stroke of the adaptor accurately administered 10-40 Units.

Example 8

Emulsions for nasal administration were prepared using the following amounts (per 1 ml) of ingredients:

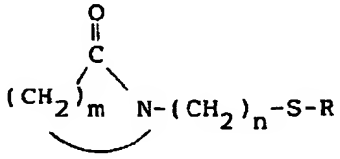
①	Salmon calcitonin	each 100, 200 and 400 Units
②	1-[2-(decylthio)ethyl] azacyclopentan-2-one	5 mg
③	dipotassium glycyrrhizate	10 mg
④	glycerol	22 mg
⑤	methyl p-oxybenzoate	1.0 mg
⑥	sodium hydroxide	to pH 6
⑦	distilled water for injection	a volume to make 1 ml

The resulting emulsions were aseptically filtered (a membrane filter of 0.22 µm), and aseptically filled in each 3 ml vials adaptable to a mechanical spray for nasal administration, to obtain the final preparation. These compositions contained 100-400 Units/ml of salmon calcitonin, and a stroke of the adaptor accurately administered 10-40 Units.

In the present invention, homogeneous and stable emulsions for nasal administration containing calcitonins are available by using an azacycloalkane derivative as the absorption promotor and glycyrrhizic acid or its non-toxic salt. The obtained emulsions exhibit satisfactory bio-availability with superior absorbability through nasal mucosa and less troubles to nasal mucosa, as compared to the conventional nasal administration preparations. Thus, the practical use of the calcitonin emulsions for nasal administration is possibilitated by the present invention.

Claims

1. A calcitonin-containing emulsion for nasal administration, which is characterized by having a calcitonin as the active ingredient, and containing, at least, an azacycloalkane derivative of the general formula [1]:



[1]

(wherein R is an alkyl residue, m is an integer of 2-4, and n is an integer of 1-15, provided that R is an alkyl residue with a carbon number of 5-11 in case where n is 1-3) as the absorption promotor, glycyrrhizic acid or its non-toxic salt, and a suitable amount of water.

2. An emulsions according to Claim 1 wherein the azacycloalkane derivative of the general formula [1] is 1-[2-(decylthio)ethyl]-azacyclopentan-2-one (wherein R is an alkyl residue with a carbon number of 10, m is 3, and n is 2).

3. An emulsion according to Claim 1 wherein the content of the calcitonin is 10-10,000 International Units per 1 ml of the emulsion.

4. An emulsion according to Claim 1 wherein the amount of glycyrrhizic acid or its non-toxic salt is 0.1-5% (W/V) per emulsion.

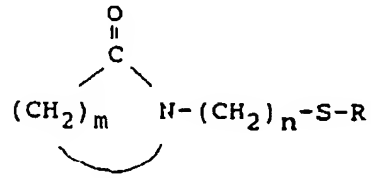
5. An emulsion according to Claim 1 wherein the amount of the azacycloalkane derivative is 0.01-10% (W/V) per emulsion.

6. An emulsion according to Claim 1 wherein the calcitonin is elcatonin, the azacycloalkane derivative is 1-

[2-(decylthio)ethyl]azacyclopentan-2-one and glycyrrhizic acid or its non-toxic salt is dipotassium glycyrrhizate.

Claims for the following Contracting States : GR And ES

1. A process for preparing a calcitonin-containing emulsion for nasal administration, characterized in that it comprises mixing a calcitonin as the active ingredient, an azacycloalkane derivative of the general formula (1):



(1)

(wherein R is an alkyl residue, m is an integer of 2-4, and n is an integer of 1-15, provided that R is an alkyl residue with a carbon number of 5-11 in case where n is 1-3) as the absorption promotor, glycyrrhizic acid or its non-toxic salt, and a suitable amount of water, and emulsifying the mixture.

2. The process of claim 1 wherein the azacycloalkane derivative of the general formula (1) is 1-[2-(decylthio)ethyl]-azacylopentan-2-one (wherein R is an alkyl residue with a carbon number of 10, m is 3, and n is 2).

3. The process of claim 1 or 2 wherein the content of the calcitonin is 10-10,000 International Units per 1 ml of the emulsion.

4. The process of claims 1 to 3 wherein the amount of glycyrrhizic acid or its non-toxic salt is 0.1-5% (W/V) per emulsion.

5. The process of claims 1-4 wherein the amount of the azacycloalkane derivative is 0.01-10% (W/V) per emulsion.

6. The process of claims 1-5 wherein the calcitonin is elcatonin, the azacycloalkane derivative is 1-[2-(decylthio)ethyl] azacyclopentan-2-one and glycyrrhizic acid or its non-toxic salt is dipotassium glycyrrhizate.

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FIG. 1

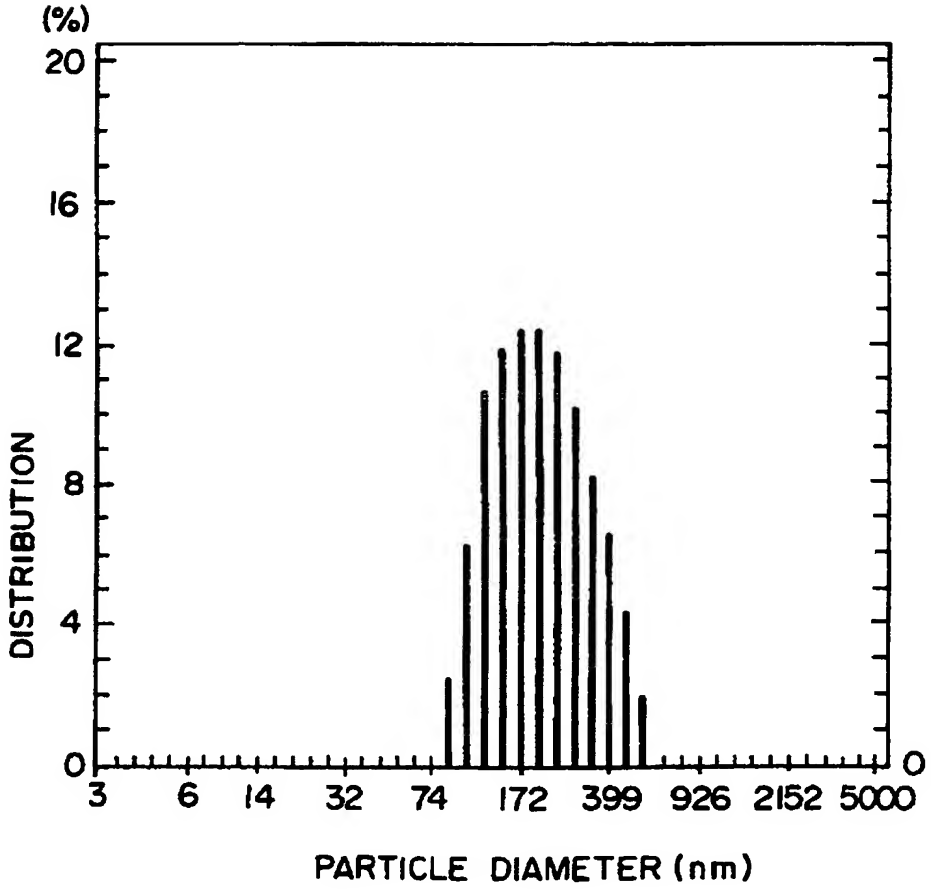
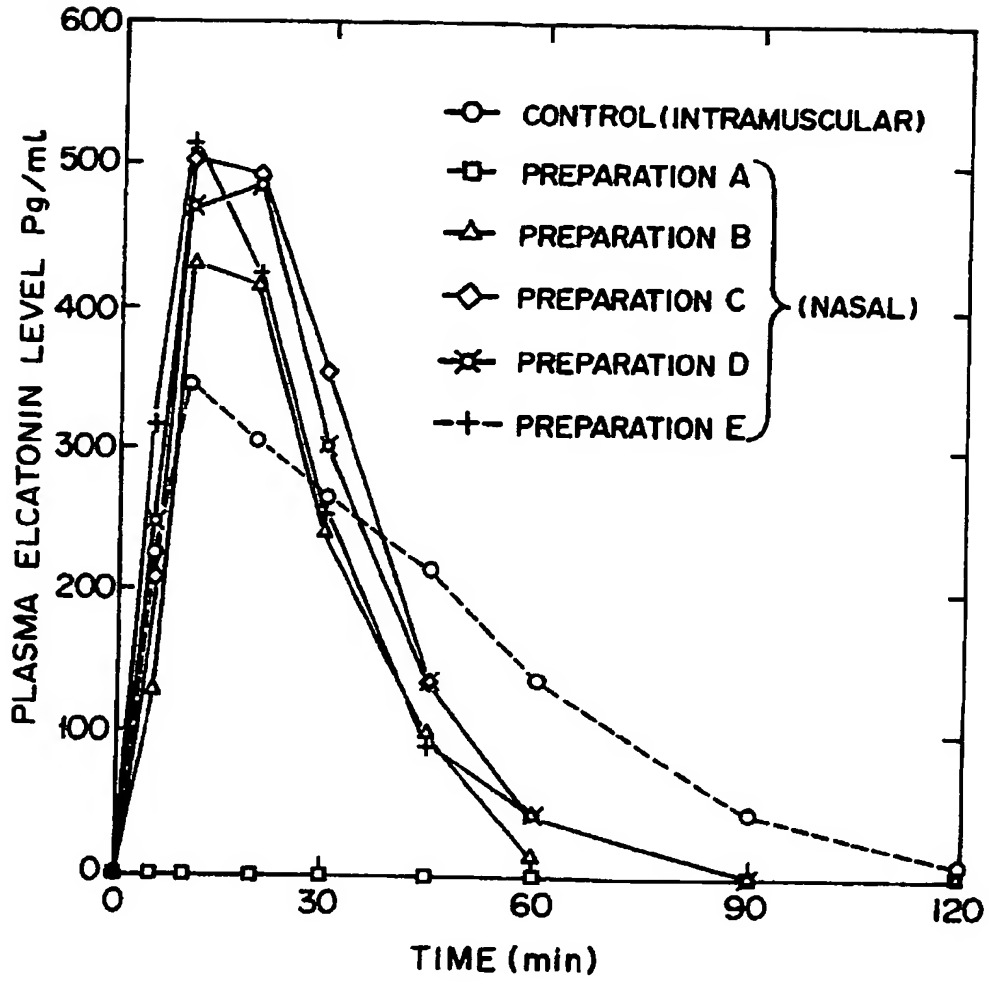

(%)
20
16
12
8
4
0
DISTRIBUTION
3
6
14
32
74
172
399
926
2152
5000
0
PARTICLE DIAMETER (nm)

FIG. 2



!DOCID: <EP_____ __0471618A1_I_>

European Patent Office

EUROPEAN SEARCH REPORT

Application Number EP 91402231.4

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,Y	PATENT ABSTRACTS OF JAPAN, unexamined applications, section C, vol. 12, no. 110, April 8, 1988 THE PATENT OFFICE JAPANESE GOVERNMENT page 159 C 486 * Kokai-no. 62-238 261 (HISAMITSU PHARMACEUT CO INC.) * --	1,2,6	A 61 K 37/30 A 61 K 9/107 A 61 K 47/22
Y	GB - A - 2 212 062 (ISF SOCIETA PER AZIONI) * Abstract; claims * --	1,2,6	
A	EP - A2 - 0 358 234 (RORER INTERNATIONAL (OVERSEAS) INC.) * Abstract * --	1	
A	EP - A2 - 0 183 527 (YAMANOUCHI PHARMACEUTICAL CO LTD.) * Abstract * --	1	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A 61 K
A	CHEMICAL ABSTRACTS, vol. 105, no. 18, November 3, 1986, Columbus, Ohio, USA T. HASUMI et al. "Nasal formulations containing calcitonin and amino acids" page 375, column 2, abstract-no. 158 833v & Jpn. Kokai Tokkyo Koho JP 61,118,325 (86,118,325) --	1	
A	CHEMICAL ABSTRACTS, vol. 109, no. 22, November 28, 1988, Columbus, Ohio, USA T. HASUMI et al. " Nasal compositions containing calci-	1	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	18-10-1991	SCHNASS

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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EUROPEAN SEARCH REPORT

Application Number

EP 91402231.4

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
	tonin" page 456, column 2, abstract-no. 197 195r & Jpn. Kokai Tokkyo Koho JP 63 10,735 (88 10,735) --		
A	CHEMICAL ABSTRACTS, vol. 110, no. 16, April 17, 1989, Columbus, Ohio, USA N. YAMAMOTO et al. "Intranasal compositions containing calcitonins or parathyroid hormones" page 414, column 2, abstract-no. 141 589a & Jpn. Kokai Tokkyo Koho JP 63,243,033 (88,243,033) ----	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
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